Systematic Review and Meta-Analysis

Medicine®

OPEN

Effects of paraoxonase 1 gene polymorphisms on heart diseases

Systematic review and meta-analysis of 64 case-control studies

Yazmín Hernández-Díaz, MD[a], Carlos Alfonso Tovilla-Zárate, PhD[b], Isela Esther Juárez-Rojop, PhD[c], Thelma Beatriz González-Castro, MD[a,*], Candelario Rodríguez-Pérez, MD[a], María Lilia López-Narváez, MD[d], José Manuel Rodríguez-Pérez, PhD[e], José Francisco Cámara-Álvarez[c]

Abstract

Background: Associations between paraoxonase 1 (*PON1*) gene polymorphisms and heart diseases (HD) risk remain inconsistent. In order to obtain address this issue we performed a meta-analysis to assess the association between the L55M and Q192R polymorphisms of *PON1* gene and heart diseases risk.

Methods: Relevant studies were enrolled by searching databases systematically. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to calculate the strength of association. Subgroup analyses were conducted for diagnostic and ethnicity. The heterogeneity among each of the studies was calculated by using Cochran Qtest and the inconsistency index (I^2), and Begg's funnel plot and Egger's tests were performed to evaluate publication bias.

Result: Sixty four studies involving a total of 19,715 cases and 33,397 controls were included in this meta-analysis. We found that the L55M polymorphism showed a significant association with heart diseases in Europeans (OR 1.44, 95%CI 1.33–1.56) and Asians (OR 1.18, 95%CI 1.03–1.35). This meta-analysis also showed a protective association of Q192R polymorphism with HD in Asian (OR 0.49, 95%CI 0.37–0.66) and African populations (OR 0.67, 95%CI 0.53–0.84). The 192R allele significantly decreased the risk of myocardial infarction (OR 0.75, 95%CI 0.57–0.99) and coronary artery disease (OR 0.91, 95%CI 0.84–0.98); however, individuals with 192Q allele had a markedly increased risk of coronary artery disease development (OR 1.38, 95%CI 1.22–1.56).

Conclusion: This study demonstrated that the genetic risk for heart diseases is associated with the *PON1* gene polymorphisms. L55M polymorphism is a risk factor and Q192R polymorphism is protective in certain populations. It is worth noting that the 192Q allele may be a risk factor to develop coronary artery disease.

Abbreviations: CAD = coronary artery disease, CHD = coronary heart disease, GRADE = grading of recommendations assessment, development and evaluation, HD = heart diseases, HWE = Hardy–Weinberg equilibrium, MI = myocardial infarction, NOS = Newcastle-Ottawa Scale, *PON1* = paraoxonase 1.

Keywords: ethnicity, heart disease, paraoxonase 1, polymorphisms, positive association, systematic review

1. Introduction

Obesity, diabetes, hypertension, alcohol, and genetic factors have an effect in the cause of heart diseases. Heart diseases (HD) such as coronary heart disease (CHD), coronary artery disease (CAD), and myocardial infarction (MI) are leading causes of morbidity and mortality globally.[1,2] To date, a low plasma concentration of high density lipoprotein (HDL) is one of the strongest risk factors for heart disease. The antioxidant activity of HDL is largely due to the paraoxonase (PON) which has the ability to metabolize lipid peroxides.[3,4] The *PON1* gene in humans is located on the long arm of chromosome 7 between q21.3 and q22.1.[5,6] PON1 is a calcium-dependent antioxidant glycoprotein with a molecular mass of 43 kDa and is found in serum as a component of the HDL. PON1 hydrolyzes organophosphate insecticides and is responsible for determining the toxicity of these compounds in mammals.[7,8]*PON1* has two polymorphisms in the coding region: L55M (163T>A) that results in a substitution from leucine (L) to methionine (M) at codon 55, and Q192R (575A>G) polymorphism that results in a substitution from glutamine (Q) to arginine (R) at position 192. The −192 position polymorphism is the major determinant of the PON1 activity, however, the −55 position polymorphism also modulates its activity.[4,9] Numerous case-control studies have been

Editor: Jacek Bil.

PROSPERO registration: CRD42016043782.

The authors declare that they have no conflicts of interest concerning this article.

[a] Juarez Autonomous University of Tabasco, Multidisciplinary Academic Division of Jalpa de Mendez Jalpa de Mendez, [b] Juarez Autonomous University of Tabasco, Multidisciplinary Academic Division of Comalcalco, Comalcalco, [c] Juarez Autonomous University of Tabasco, Academic Sciences Division Health, Villahermosa, Tabasco, [d] Yajalón General Hospital, Ministry of Health, Yajalón, Chiapas, [e] National Institute of Cardiology "Ignacio Chavez", Department of Molecular Biology, Mexico City, Mexico.

[*] Correspondence: Thelma Beatriz González Castro, Academic Division Multidisciplinary Jalpa de Méndez, Road Nacajuca-Jalpa de Mendez, Rancheria Rivera Alta, P.C. 86205, Jalpa de Mendez, Tabasco, Mexico (e-mail: thelma.glez.castro@gmail.com).

Medicine (2016) 95:44(e5298)

Received: 25 August 2016 / Received in final form: 4 October 2016 / Accepted: 11 October 2016

http://dx.doi.org/10.1097/MD.0000000000005298

Table 1

Individual characteristics of the studies included in this meta-analysis.

Author	Year	Ethnicity	Diagnosis	Genotype method	Sample size	Allele		Gender		p HWE	Grade quality	NOS score
						Cases	Control	Cases	Control			
					Cases/Control	L/M-Q/R	L/M-Q/R	M/F	M/F	Cases/Control		
L55M Polymorphism												
Zama, T.[9]	1997	Asian	CAD	PCR	75/115	140/10	209/21	—	—	1.00/0.59	Moderate	8
Hasselwander, O.[12]	1999	European	CHD	PCR-RFLP	103/388	133/73	501/275	70/33	234/154	0.28/0.26	Moderate	7
Ayub, A.[13]	1999	European	MI	PCR-RFLP	50/48	71/29	60/36	38/12	37/11	0.29/0.36	Moderate	7
Heijmans, B.T.[14]	2000	European	CHD	PCR-RFLP	364/250	472/256	317/183	115/249	139/111	0.20/0.78	High	7
Imai, Y.[10]	2000	Asian	CAD	PCR-FRLP	210/431	387/33	797/65	184/26	321/110	0.36/0.08	Moderate	7
Sen-Banerjee, S.[15]	2000	American	MI	PCR-RFLP	492/518	255/729	272/764	251/241	254/264	0.55/0.17	Moderate	6
Mackness, B.[16]	2001	European	CHD	PCR-RFLP	417/282	538/296	360/204	302/115	147/135	0.39/0.01	High	8
Arca, M.[17]	2002	European	CAD	PCR	585/178	726/438	233/123	413/180	84/94	0.18/1.00	High	7
Ferré, N.[18]	2002	European	MI	PCR-RFLP	215/215	263/167	263/167	215/0	215/0	0.56/0.11	Moderate	8
Yamada, Y.[19]	2002	Asian	MI	PCR	445/464	837/53	868/60	—	—	0.38/0.24	Moderate	7
Robertson, K.S.[20]	2003	European	CHD	PCR-RFLP	172/2211	227/117	2942/1480	172/0	2211/0	0.30/0.89	Moderate	7
Oliveira, S.A.[21]	2004	American	CAD	PCR-RFLP	377/379	497/257	485/273	232/119	244/132	0.00/0.37	Moderate	7
Tobin, M.D.[22]	2004	European	MI	PCR-RFLP	547/505	682/412	643/367	372/175	313/192	0.12/0.92	Moderate	7
Martinelli, N.[23]	2005	European	CAD	PCR	642/273	795/489	328/218	520/122	187/86	0.15/0.70	Moderate	7
Kerkeni, M.[24]	2006	African	CAD	PCR-RFLP	100/120	151/49	181/59	74/26	87/33	1.00/0.04	Moderate	7
Blatter Garin, M.C.[25]	2006	European	CAD	—	710/199	846/574	261/137	564/146	100/99	0.69/0.52	Moderate	7
Rios, D.L.[26]	2007	American	CAD	PCR-RFLP	296/141	349/243	152/130	196/100	65/76	0.00/0.00	Moderate	7
Rios, D.L.[26]	2007	African	CAD	PCR-RFLP	148/127	196/100	166/88	99/49	56/71	0.00/0.03	Moderate	7
Saeed, M.[27]	2007	Asian	MI	PCR-RFLP	201/350	322/80	548/152	153/58	258/112	0.00/0.11	Moderate	7
Troughton, J.A.[28]	2008	European	CHD	PCR	433/247	329/165	559/307	433/0	247/0	0.66/0.46	Moderate	8
Özkök, E.[29]	2008	European	CAD	PCR-RFLP	139/119	167/111	104/134	110/29	86/33	0.85/0.00	High	7
Birjmohun, R.S.[30]	2009	European	CAD	AS-PCR	1091/2116	1334/766	2670/1458	655/436	1270/846	9.49/0.59	Moderate	8
Agrawal, S.[3]	2009	Asian	CAD	PCR-RFLP	279/190	412/146	262/118	244/41	163/37	0.08/0.23	Moderate	6
Kaman, D.[31]	2009	European	CAD	PCR-RFLP	277/92	369/185	103/81	188/89	54/38	1.00/0.67	Moderate	7
Koubaa, N.[32]	2009	African	CAD	Multiplex PCR	91/118	127/55	183/53	64/27	59/59	0.45/0.42	Moderate	7
Aydin, M.[33]	2009	European	CAD	PCR	218/131	287/155	129/143	—	—	0.76/0.00	Moderate	6
Mukamal, K.J.[34]	2009	American	MI	Taqman	482/971	616/384	1251/691	263/243	528/490	0.84/0.40	Moderate	7
Lakshmy, R.[35]	2010	Asian	MI	PCR-RFLP	124/154	201/47	239/69	108/16	169/25	0.56/0.03	Moderate	7
Gupta, N.[36]	2011	Asian	CAD	PCR-FRLP	350/300	593/107	487/113	286/64	151/149	0.09/0.09	Moderate	7
Bounafaa, A.[37]	2015	African	ACS	PCR	205/100	257/153	146/54	125/80	52/48	0.23/0.61	High	7
Q192R Polymorphism												
Serrato, M.[38]	1995	American	CAD	PCR	223/247	251/195	339/155	158/65	104/143	0.58/0.30	Moderate	6
Antikainen, M.[39]	1996	European	CAD	PCR	380/169	562/198	249/89	380/0	78/91	0.42/0.07	Moderate	6
Suehiro, T.[40]	1996	Asian	CHD	PCR-RFLP	134/252	107/162	192/312	86/48	132/120	0.71/0.59	Moderate	7
Herrmann, S.M.[41]	1996	European	MI	PCR-ASO	642/701	882/402	989/413	642/0	701/0	0.46/0.01	Moderate	7
Suehiro, T.[40]	1996	Asian	MI	PCR-RFLP	91/252	73/109	192/312	—	132/120	1.00/0.59	Moderate	7
Zama, T.[9]	1997	American	CAD	PCR	75/115	39/111	95/135	—	—	0.36/0.44	Moderate	8
Odawara M.[42]	1997	Asian	CHD	PCR	42/122	26/58	103/141	22/20	67/55	0.06/0.26	Moderate	7
Ombres, D.[43]	1998	European	CAD-MI	PCR	472/204	657/287	296/112	330/142	—	0.82/0.72	Moderate	7
Pati, N.[44]	1998	Asian	CAD	PCR	120/80	130/110	132/28	—	—	0.06/0.00	Moderate	7
Sanghera, D.K.[45]	1998	Asian	CHD	PCR	157/190	169/145	258/122	115/14	144/45	0.33/0.24	Moderate	6
Pfohl, M.[46]	1999	European	CAD	PCR	170/119	223/117	176/60	—	—	1.00/0.81	Moderate	8

(*continued*)

Table 1

(continued).

Author	Year	Ethnicity	Diagnosis	Genotype method	Sample size	Allele		Gender		p HWE	Grade quality	NOS score
						Cases	Control	Cases	Control			
					Cases/Control	L/M-Q/R	L/M-Q/R	M/F	M/F	Cases/Control		
Hasselwander, O.[12]	1999	European	CAD	PCR-RFLP	103/388	144/62	534/242	70/33	234/154	1.00/0.19	Moderate	7
Ayub, A.[13]	1999	European	MI	PCR-RFLP	50/48	69/31	76/0	38/12	37/11	0.33/0.39	Moderate	7
Imai, Y.[10]	2000	Asian	CAD	PCR-RFLP	210/431	107/313	300/562	184/26	321/110	0.10/0.16	Moderate	7
Aynacioglu, A.S.[47]	2000	Asian	CAD	PCR-RFLP	96/105	120/72	145/65	74/22	77/28	0.38/0.65	Moderate	7
Heijmans, B.T.[14]	2000	European	CHD	PCR	364/250	437/171	358/142	115/249	139/111	0.04/0.75	High	7
Sen-Banerjee, S.[15]	2000	American	MI	PCR-RFLP	492/518	717/267	784/252	251/241	254/264	0.00/0.00	Moderate	6
Aubo, C.[48]	2000	European	MI	—	156/310	228/84	431/189	140/16	262/48	0.83/0.28	Moderate	7
Osei-Hyiaman, D.[49]	2001	Asian	CAD	PCR	201/231	315/87	406/56	121/80	135/96	0.00/0.11	Moderate	8
Mackness, B.[16]	2001	European	CHD	PCR-RFLP	417/282	594/240	414/150	302/115	147/135	0.62/0.00	High	8
Sentí, M.[8]	2001	European	MI	PCR	280/396	387/173	551/241	253/27	264/132	0.16/0.72	Moderate	7
Turban, S.[50]	2001	American	MI	PCR-RFLP	13/301	21/5	415/187	—	—	1.00/0.04	Moderate	7
Ferré, N.[18]	2002	European	MI	PCR-RFLP	215/215	297/133	305/125	215/0	215/0	0.42/0.61	Moderate	8
Yamada, Y.[19]	2002	Asian	MI	PCR	1035/1168	1367/703	1566/770	—	—	0.00/0.89	Moderate	7
Scacchi, R.[51]	2003	European	CAD	PCR	200/643	308/92	976/310	144/56	286/357	0.10/0.16	Moderate	6
Zee, R.Y.[52]	2003	European	CAD	PCR-RFLP	347/437	496/188	627/247	305/37	382/59	0.58/0.81	Moderate	7
Kuremoto, K.[11]	2003	Asian	CAD	PCR-RFLP	124/55	109/139	35/75	124/0	55/0	0.14/0.00	Moderate	7
Robertson, K.S.[20]	2003	European	CHD	PCR-RFLP	184/2424	269/99	3438/1410	184/0	2424/0	0.57/0.99	Moderate	7
Wang, X.[53]	2003	Asian	MI	PCR-RFLP	474/475	378/570	334/616	474/0	475/0	0.38/0.19	Moderate	7
Oliveira, S.A.[21]	2004	American	CAD	PCR-RFLP	351/376	484/218	494/258	232/119	244/132	0.90/0.64	Moderate	7
Lacinski, M.[54]	2004	European	CAD	PCR-RFLP	51/60	84/18	88/32	40/11	35/25	1.00/0.31	Moderate	8
Tobin, M.D.[22]	2004	European	MI	PCR-RFLP	547/505	788/306	733/277	372/175	313/192	0.13/0.31	Moderate	7
Lacinski, M.[54]	2004	European	MI	PCR-RFLP	73/60	100/46	88/32	57/16	35/25	0.78/0.31	Moderate	8
Martinelli, N.[23]	2005	European	CAD	PCR	642/273	906/378	388/158	520/122	187/86	0.21/0.46	Moderate	7
Kerkeni, M.[24]	2006	African	CAD	PCR-RFLP	100/120	155/45	195/45	74/26	87/33	0.25/0.56	Moderate	7
Blatter Garin, M.C.[25]	2006	European	CAD	—	710/199	1038/382	265/133	564/146	100/99	0.25/1.00	Moderate	7
Ameno, K.[55]	2006	Asian	CHD	PCR-RFLP	81/84	85/77	79/89	—	—	0.11/0.13	Moderate	8
Baum, L.[56]	2006	Asian	MI	PCR	231/310	167/295	265/355	189/42	144/166	0.03/0.06	Moderate	8
Rios, D.L.[26]	2007	American	CAD	PCR-RFLP	296/141	369/223	189/93	196/100	65/76	0.00/0.00	Moderate	7
Rios, D.L.[26]	2007	African	CAD	PCR-RFLP	148/127	165/131	130/124	99/49	56/71	0.00/0.05	Moderate	7
Saeed, M.[27]	2007	Asian	MI	PCR-RFLP	203/349	252/154	469/229	153/58	258/112	0.37/0.03	Moderate	7
Balcerzyk, A.[57]	2008	European	CAD	PCR-RFLP	178/180	278/78	243/117	117/61	128/52	0.66/0.17	Moderate	8
Özkök, E.[29]	2008	Asian	CAD	PCR-RFLP	139/119	144/134	164/74	110/29	86/33	0.73/0.28	High	7
Bhattacharyya, T.[58]	2008	American	CAD	Taqman	962/405	1332/592	529/281	—	—	1.00/0.44	Moderate	6
Gamboa, R.[59]	2008	American	CHD	PCR	155/155	171/139	178/132	66/89	71/84	0.05/0.86	Moderate	7
Birjmohun, R.S.[30]	2009	European	CAD	AS-PCR	1091/2116	1583/599	3031/1201	655/436	1270/846	0.14/0.48	Moderate	8
Agrawal, S.[3]	2009	Asian	CAD	PCR-RFLP	275/195	280/270	224/166	244/0	163/0	0.54/0.07	Moderate	6
Kaman, D.[31]	2009	Asian	CAD	PCR-RFLP	277/92	348/206	127/57	188/89	54/38	0.05/0.80	Moderate	7
Koubaa, N.[32]	2009	African	CAD	Multiplex PCR	91/118	134/48	187/49	64/27	59/59	1.00/1.00	Moderate	7
Aydin, M.[33]	2009	Asian	CAD	PCR	218/131	210/226	169/93	–	–	0.58/0.01	Moderate	6
Mukamal, K.J.[34]	2009	American	MI	Taqman	488/984	699/277	1400/568	263/243	528/490	0.82/0.01	Moderate	
Izar, M.C.[60]	2009	American	MI	PCR-RFLP	386/604	460/312	700/508	228/158	186/418	0.00/0.00	Moderate	7
Mohamed, R.H.[61]	2010	Asian-African	CAD	PCR	150/50	92/208	63/37	119/31	26/24	0.12/0.06	Moderate	7
Lakshmy, R.[35]	2010	Asian	MI	PCR-RFLP	124/221	154/94	316/126	108/16	169/25	0.03/0.13	Moderate	7

(*continued*)

Table 1
(continued).

Author	Year	Ethnicity	Diagnosis	Genotype method	Sample size	Allele		Gender		p HWE		Grade quality	NOS score
						Cases	Control	Cases	Control				
					Cases/Control	L/M-Q/R	L/M-Q/R	M/F	M/F	Cases/Control			
Gupta, N.[36]	2011	Asian	CAD	PCR-RFLP	350/300	424/276	444/156	286/64	151/149	0.82/0.29		Moderate	7
Luu, H.N.[62]	2011	American	CHD	TaqMan	1469/8501	2007/851	12036/4966	—	—	0.00/0.10		Moderate	7
Luu, H.N.[62]	2011	African-American	CHD	TaqMan	440/3150	282/598	2174/4126	—	—	0.58/0.74		Moderate	7
Elnoamany, M.F.[63]	2012	Asian-African	CAD	PCR-RFLP	95/85	95/95	131/39	69/26	63/22	0.00/0.35		Moderate	8
Bayrak, A.[64]	2012	Asian	CAD	PCR-RFLP	102/106	143/61	156/56	88/40	60/82	0.47/0.31		Moderate	7
Hassan, M.A.[65]	2013	Asian	CAD	PCR-RFLP	121/108	137/105	157/59	71/50	40/68	0.71/0.15		Moderate	7
Kang, Y.H.[66]	2013	Asian	CAD	TaqMan	515/537	674/356	700/374	449/66	375/162	0.06/0.04		High	8
Hampe, M.H.[67]	2014	Asian	CAD	–	60/60	72/48	72/48	31/29	31/29	1.00/0.43		Moderate	7
El-Lebedy, D.[68]	2014	Asian-African	CAD	TaqMan	134/50	179/89	78/22	88/46	27/23	1.00/0.04		Moderate	7
Rahman, M.F.[69]	2015	Asian-Africa	MI	PCR-RFLP	102/72	128/76	114/30	66/36	59/13	0.67/0.06		Moderate	7
Han, Y.[70]	2015	Asian	CHD	GWAS	688/1226	456/920	808/1644	445/243	776/450	0.05/0.24		Moderate	7
Bounafaa, A.[37]	2015	African	ACS	PCR	205/100	293/117	151/49	125/80	52/48	0.00/0.78		High	7

ACS = acute coronary syndrome, CAD = coronary artery disease, CHD = coronary heart disease, HWE = Hardy-Weinberg equilibrium, MI = myocardial infarction, NOS = Newcastle-Ottawa Scale.

conducted to determine whether the *PON1* 55M or 192R alleles are closely associated with HD; some of them have found an association between the polymorphism and the disease[3,10,11] while others have not.[3,4] In this study, we performed a meta-analysis which is a very useful tool to combine information from different sources, by pooling 64 case-control studies to comprehensively determine the overall strength of associations between *PON1* polymorphisms (L55M and Q192R) and the susceptibility to develop heart diseases.

2. Methods

This meta-analysis was designed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA Compliant) statement. The protocol of the systematic review was registered in PROSPERO (http://www.crd.york.ac.uk/prospero/) with registration number: CRD42016043782. Ethics approval was not necessary for this study, due to only data from individual studies were analyzed.

2.1. The literature search

The search for all the studies investigating the association of the *PON1* polymorphism with HD risk was conducted through a systematic computerized literature search from PubMed and EBSCO databases prior to July 2016 using the following search terms: ("paraoxonase1" or "*PON1*") and ("L55M polymorphism" or "Q192R polymorphism") and ("heart disease" or "coronary heart disease" or "coronary artery disease" or "myocardial infarction"). We also conducted a manual search to find other potential articles based on references identified in individual articles.

2.2. Inclusion and exclusion criteria

As a prerequisite, the selection of studies in our meta-analysis was abided by the predefined inclusion and exclusion criteria: the study investigated the association between the *PON1* polymorphisms and heart disease; the study included patients diagnosed with any heart disease; the study used healthy subjects as controls; provided sufficient data on allele or genotype distribution in patients and controls; the study was written in English; the study had been published in peer-reviewed journals. The exclusion criteria were: studies without control population; to be comments, review articles, meta-analysis, or articles only with an abstract.

2.3. Data extraction and methodological assessment

To make sure of the accuracy of the information, data extraction was performed independently by two authors (YHD and CRP) on the basis of a standard protocol including the following elements: publication year, the first author's surname, geographical location, design of study, total number of cases and controls, mean age, sex, genotype frequencies, and genotyping method. Any encountered discrepancies were adjudicated by a discussion until a consensus was reached. The quality of each selected study was assessed independently by the same two authors according to the Newcastle-Ottawa Scale (NOS). The study quality was evaluated based on 8 items and assigned a quality score that ranged from 0 to 9 points. The NOS criteria included three aspects selection: 0 to 4; comparability: 0 to 2; and outcome: 0 to 3. The quality of the body of evidence for each determinant was examined according to the grading of recommendations assessment, development, and evaluation (GRADE). The overall quality was determined to be high, moderate, low, or very low

Table 2

Results of meta-analysis for PON1 polymorphisms and risk of heart diseases by sub-groups.

Genetic model	Group	OR (95% CI)	Cochran *Q* test	I^2 (%)	Egger's test
L55M					
Allelic		1.01 (0.96–1.08)	0.095	27	0.175
Homozygote		0.98 (0.87–1.11)	0.197	18	0.986
Heterozygote	HD	1.02 (0.95–1.09)	0.407	3	0.242
Dominant		0.99 (0.88–1.11)	0.297	11	0.721
Recessive		1.04 (0.97–1.13)	0.077	28	0.091
Allelic		1.03 (0.92–1.15)	0.966	0	0.698
Homozygote		1.05 (0.82–1.34)	0.769	0	0.404
Heterozygote	CHD	1.04 (0.89–1.22)	0.579	0	0.095
Dominant		1.02 (0.81–1.29)	0.466	0	0.256
Recessive		1.05 (0.90–1.22)	0.844	0	0.075
Allelic		1.01 (0.92–1.11)	0.807	37	0.514
Homozygote		0.96 (0.78–1.18)	0.131	31	0.708
Heterozygote	CAD	1.03 (0.94–1.12)	0.688	0	0.103
Dominant		0.96 (0.82–1.11)	0.413	2	0.495
Recessive		1.10 (0.97–1.23)	0.068	0	0.060
Allelic		1.00 (0.92–1.09)	0.806	0	0.100
Homozygote		0.92 (0.75–1.13)	0.965	0	0.417
Heterozygote	MI	1.03 (0.87–1.21)	0.162	33	0.383
Dominant		0.99 (0.85–1.17)	0.891	0	0.889
Recessive		1.02 (0.89–1.16)	0.328	12	0.238
Allelic		0.99 (0.92–1.09)	0.162	28	0.111
Homozygote		1.20 (0.93–1.54)	0.122	0	0.106
Heterozygote	European	0.99 (0.84–1.18)	0.532	32	0.255
Dominant		0.98 (0.90–1.07)	0.105	0	0.232
Recessive		1.44 (1.33–1.56)	0.666	0	0.274
Allelic		1.18 (1.03–1.35)	0.929	0	0.577
Homozygote		1.33 (0.85–2.07)	0.984	0	0.159
Heterozygote	Asian	1.20 (1.02–1.41)	0.881	0	0.859
Dominant		1.23 (0.79–1.89)	0.987	0	0.226
Recessive		1.21 (1.03–1.41)	0.880	0	0.942
Allelic		0.81 (0.62–1.06)	0.136	27	0.853
Homozygote		0.51 (0.26–1.01)	0.151	31	0.175
Heterozygote	African	0.91 (0.64–1.29)	0.881	16	0.491
Dominant		0.57 (0.32–1.01)	0.237	29	0.088
Recessive		0.83 (0.58–1.19)	0.116	0	0.900
Allelic		1.03 (0.93–1.14)	0.505	0	0.079
Homozygote		1.01 (0.81–1.26)	0.457	0	0.825
Heterozygote	American	1.01 (0.82–1.25)	0.231	30	0.877
Dominant		1.05 (0.89–1.24)	0.891	0	0.695
Recessive		1.03 (0.85–1.25)	0.244	27	0.768
Q192R					
Allelic		0.96 (0.83–1.02)	0.103	11	0.182
Homozygote		0.92 (0.84–1.01)	0.271	10	0.209
Heterozygote	HD	0.99 (0.93–1.05)	0.206	14	0.064
Dominant		0.92 (0.84–1.00)	0.064	24	0.055
Recessive		0.96 (0.91–1.02)	0.196	15	0.129
Allelic		0.97 (0.91–1.03)	0.535	0	0.944
Homozygote		0.85 (0.71–1.02)	0.138	32	0.653
Heterozygote	CHD	0.97 (0.85–1.11)	0.182	29	0.462
Dominant		0.93 (0.83–1.04)	0.352	0	0.820
Recessive		0.98 (0.90–1.07)	0.421	0	0.701
Allelic		0.91 (0.84–0.98)	0.272	15	0.023
Homozygote		0.73 (0.60–0.88)	0.119	25	0.293
Heterozygote	CAD	0.98 (0.89–1.09)	0.231	16	0.011
Dominant		1.38 (1.22–1.56)	0.775	0	0.228
Recessive		0.88 (0.79–0.99)	0.173	23	0.045
Allelic		0.93 (0.86–1.00)	0.151	25	0.520
Homozygote		0.75 (0.57–0.99)	0.053	46	0.709
Heterozygote	MI	0.92 (0.82–1.04)	0.090	38	0.420
Dominant		0.70 (0.50–0.99)	0.140	37	0.485
Recessive		0.85 (0.75–0.97)	0.108	37	0.075
Allelic		1.01 (0.95–1.07)	0.401	0	0.814
Homozygote		0.98 (0.83–1.15)	0.062	30	0.723
Heterozygote	European	1.04 (0.96–1.14)	0.188	20	0.382
Dominant		0.94 (0.83–1.07)	0.415	0	0.940
Recessive		1.03 (0.95–1.13)	0.078	25	0.582
Allelic		0.74 (0.67–0.83)	0.306	14	0.701
Homozygote		0.48 (0.35–0.65)	0.079	39	0.106
Heterozygote	Asian	0.49 (0.37–0.66)	0.136	36	0.267
Dominant		0.66 (0.53–0.82)	0.120	33	0.588
Recessive		0.69 (0.57–0.84)	0.150	31	0.179
Allelic		0.67 (0.53–0.84)	0.320	14	0.182
Homozygote		0.51 (0.29–0.90)	0.953	0	0.317
Heterozygote	African	0.76 (0.49–1.18)	0.091	23	0.085
Dominant		0.45 (0.30–0.68)	0.419	0	0.074
Recessive		0.72 (0.52–1.00)	0.252	25	0.025
Allelic		0.98 (0.91–1.06)	0.306	15	0.649
Homozygote		1.02 (0.84–1.24)	0.253	22	0.152
Heterozygote	American	0.93 (0.81–1.08)	0.067	40	0.478
Dominant		1.03 (0.85–1.25)	0.077	40	0.213
Recessive		0.95 (0.84–1.08)	0.122	38	0.753

CAD = coronary artery disease, CHD = coronary heart disease, CI = confidence interval, HD = heart disease, MI = myocardial infarction, OR = odds ratio, *PON1* = paraoxonase 1.

using a stepwise, structural methodology (Table 1). Any discrepancies were resolved as described above.

2.4. Statistical analysis

The genotype frequencies of the polymorphism among the cases and controls of all of the included studies were assessed under the Hardy–Weinberg equilibrium (HWE) using the chi-squared goodness-of-fit test (Table 1). Odds ratios (ORs) with 95% confidence interval (CI) were calculated to assess the intensity of the association between the PON1 L55M and Q192R polymorphisms and heart diseases. We assessed the association between the polymorphisms and HD using five genetic models: allelic model (A vs. G), homozygote model (AA vs. GG), heterozygote model (AG vs. GG), dominant model (AA/AG vs. GG), and recessive model (AA vs. AG/GG). The heterogeneity among studies was appraised by the Cochran Q test and the inconsistency index (I^2); if Q test was significant ($P<0.05$) or the I^2 test exhibited $>50\%$ (which indicates significant heterogeneity), then the random-effect model was conducted or else the fixed-effects model was used. Subgroup analyses were further performed according to primary outcome (CHD, CAD, and MI) and to ethnicity (European, Asian, African, and American). In order to evaluate the influence of single studies on the overall estimate, a sensitivity analysis was performed. Finally, we constructed funnel plots and performed Egger's test for publication bias by inspecting the symmetry of funnel plots. Publication bias was considered present with $P<0.05$. All statistical analyses were conducted using the Comprehensive meta-analysis software (Comprehensive Meta Analysis software Version 2, Biostat Inc., NJ, United States).

3. Results

3.1. Literature search and study characteristics

Through a literature searching, our search yielded 308 published studies, of which 206 studies were excluded as they did not investigate the association of *PON1* polymorphism with heart

diseases. After the subsequent reviewing of the remaining 80 articles, 16 not case-control studies were also excluded. Therefore, only 64 studies qualifying our strict selection criteria were involved in this meta-analysis.[3,8–70] We established a database of the extracted information from each eligible article (Table 1).

3.2. Association of L55M polymorphism and the risk of heart diseases

The association between L55M polymorphism and the risk to heart diseases was analyzed in 30 studies involving 9838 HD patients and 11,732 healthy controls; there was no statistical evidence of association between the L55M polymorphism and an overall risk of heart disease (Table 2). In the sub-group analysis stratified by diagnostic, no association among this polymorphism and CHD, CAD, or MI was observed in all genetic models (Table 2). When performing a meta-analysis by ethnicity, higher risk was detected in European (recessive model: OR 1.44, 95%CI 1.33–1.56) and Asian populations (allelic model: OR 1.18, 95% CI 1.03–1.35; heterozygote model: OR 1.20, 95%CI 1.02–1.41; and recessive model: OR 1.21, 95%CI 1.03–1.41), but not in African or Mexican populations (Figs. 1 and 2; Table 2).

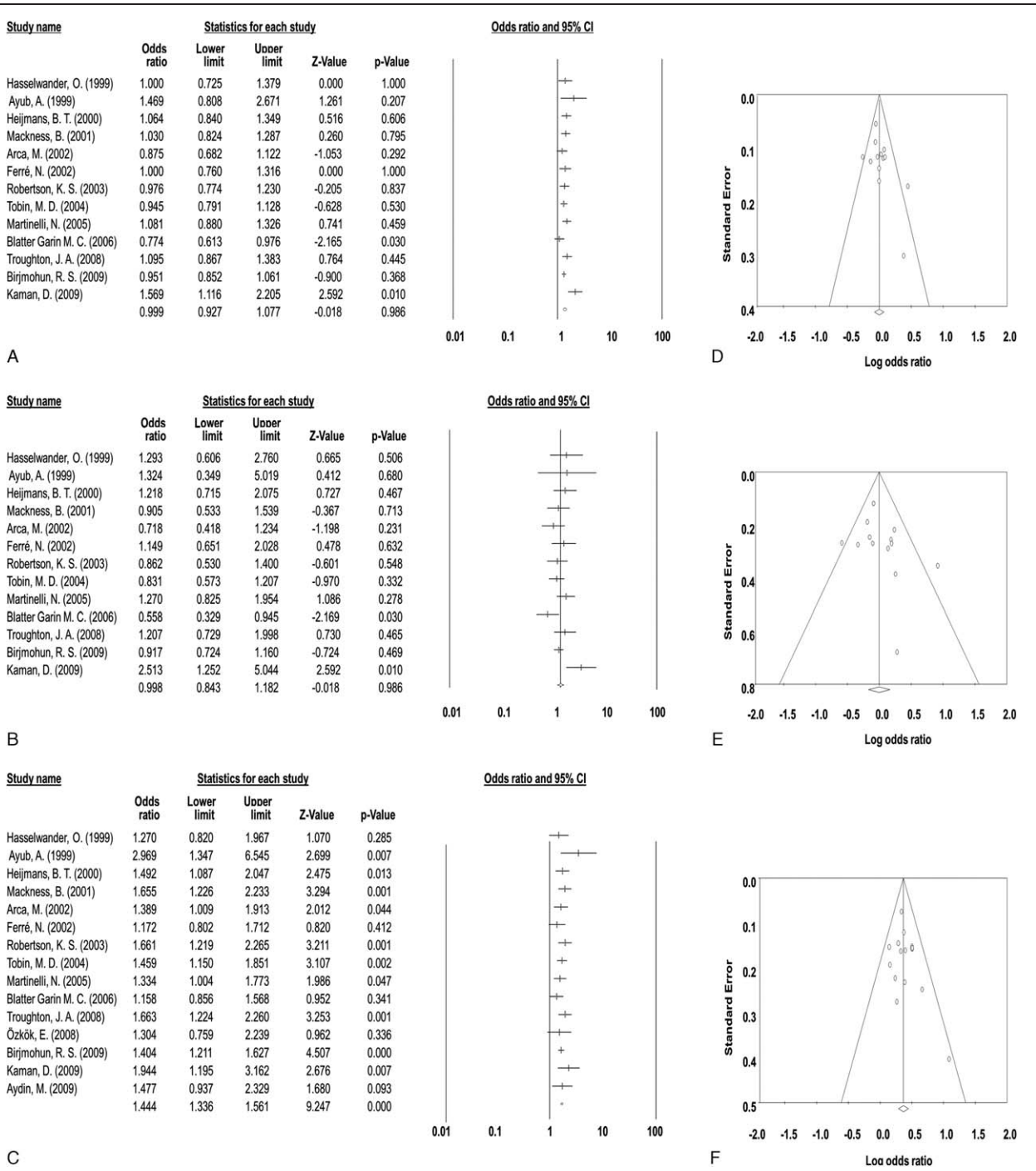

Figure 1. Results of analysis in European population for L55M polymorphism. A, B, and C showing the forest plot for genetic models: allelic, homozygote, and recessive, respectively; D, E, and F showing the funnel plot of publication biases with the genetic models above mentioned.

3.3. Association of Q192R polymorphism and the risk of heart diseases

A total of 64 studies with 19,715 patients and 33,397 controls were eligible for the pooled analysis of Q192R polymorphism. Overall, no significant association was found between the *PON1* gene Q192R polymorphism and heart diseases risk. The main results of meta-analysis are shown in Table 2. However, in the stratification analysis by diagnostic type, a significantly decreased risk of CAD (allelic model: OR 0.91, 95%CI 0.84–0.98; homozygote model: OR 0.73, 95%CI 0.60–0.88; and recessive model: OR 0.88, 95% CI 0.79–0.99) and MI (homozygote model: OR 0.75, 95%CI 0.57–0.99; dominant model: OR 0.70, 95%CI 0.50–0.99; and recessive model: OR 0.85, 95%CI 0.75–0.97) was identified (Figs. 3 and 4; Table 2). Moreover, in coronary artery diseases, subjects with a Q allele had a markedly increased risk of developing the disease (dominant model: OR 1.38, 95%CI 1.22–1.56). No association was observed in CHD population (Fig. 3; Table 2). In a stratified analysis by specific ethnicity, the Q192R polymorphism had a protective effect under all genetic models in Asian (allelic model: OR 0.74, 95%CI 0.67–0.83; homozygote model: OR 0.48, 95%CI 0.35–0.65; heterozygote model: OR 0.49, 95%CI 0.37–0.66; dominant model: OR 0.66, 95%CI 0.53–0.84; and recessive model: OR 0.69, 95%CI 0.57–0.84) and African populations under allelic, homozygote and dominant models: OR 0.67, 95%CI 0.53 to 0.84; OR 0.51, 95%CI 0.29 to 0.90; OR 0.45, 95%CI 0.30 to 0.68 (Figs. 5 and 6; Table 2). No relationship was found between the polymorphism and the disease in European or American populations (Table 2).

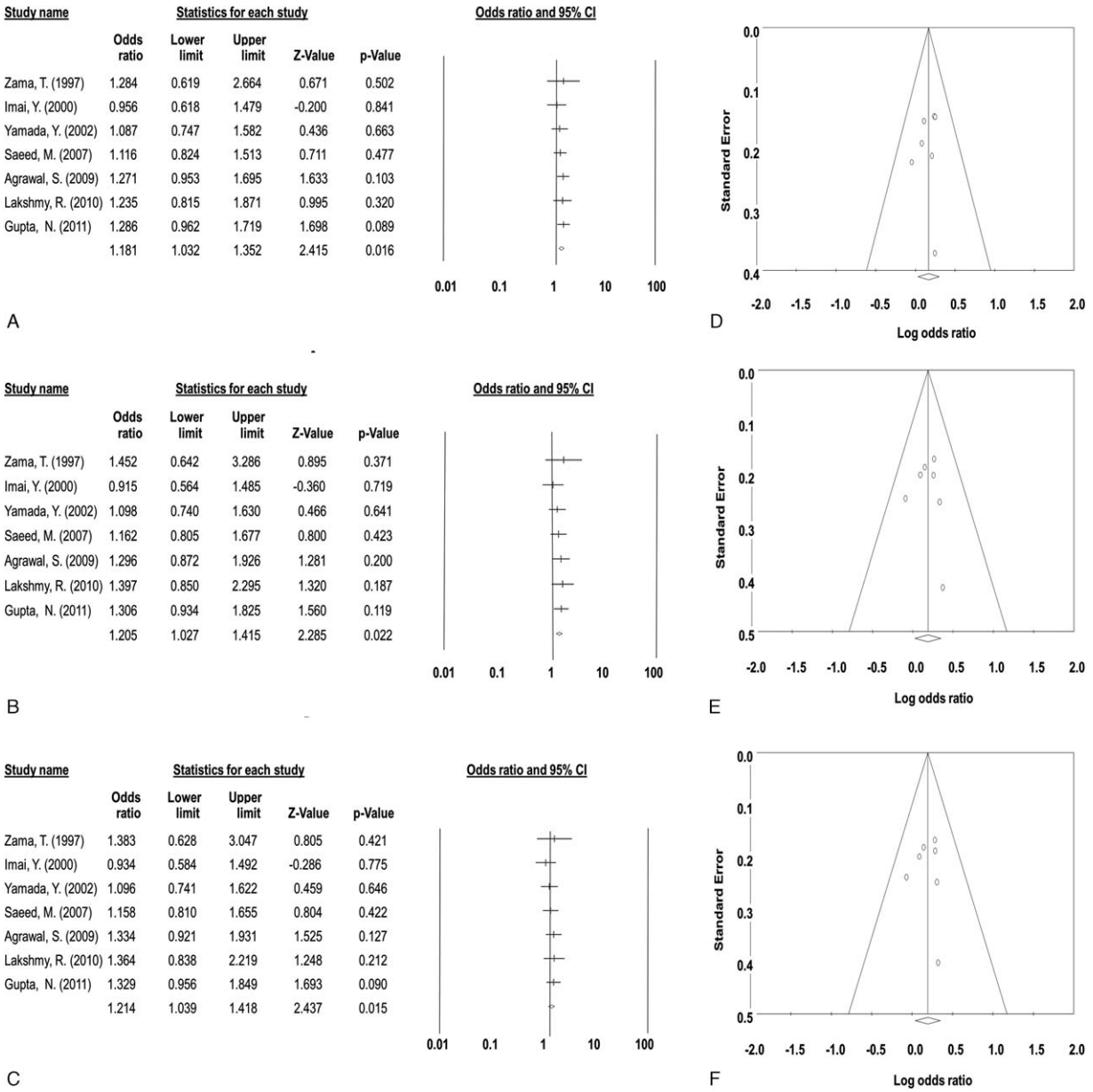

Figure 2. Results of analysis in Asian population for L55M polymorphism. A, B, and C showing the forest plot for genetic models: allelic, heterozygote, and recessive, respectively; D, E, and F showing the funnel plot of publication biases with the genetic models above mentioned.

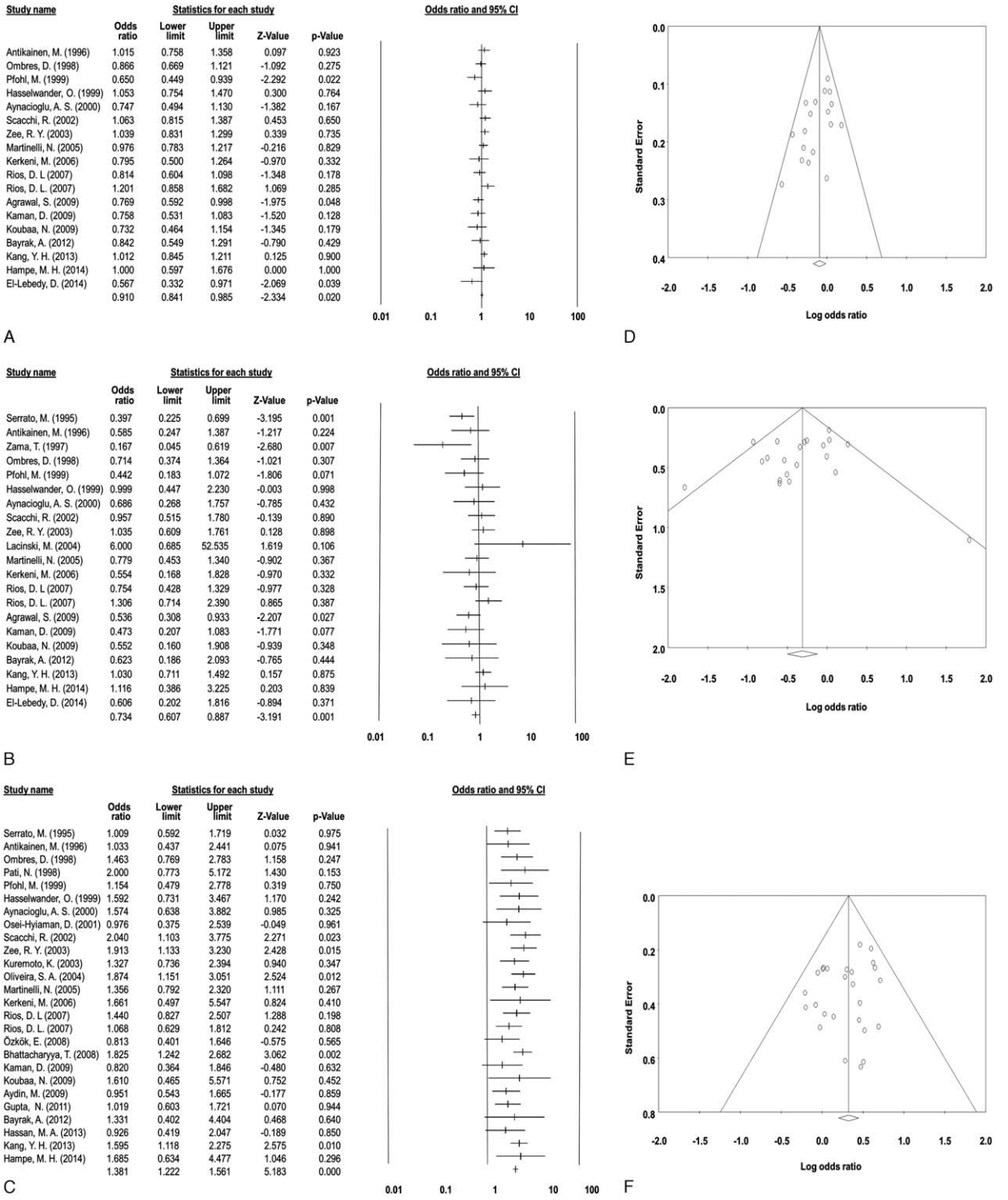

Figure 3. Results of analysis in CAD population for Q192R polymorphism. A, B, and C showing the forest plot for genetic models: allelic, homozygote, and dominant, respectively; D, E, and F showing the funnel plot of publication biases with the genetic models above mentioned. CAD = coronary artery disease.

3.4. Test for heterogeneity and sensitivity analyses

The subgroup analysis revealed no significant heterogeneity among studies (Table 2). In the sensitivity analyses, the influence of each study on the pooled OR was checked by excluding 1 study each time. If the exclusion of any single study did not alter the significance of the final decision, it suggested that the outcomes were robust. The corresponding pooled ORs were not materially altered, confirming that our results were statistically robust.

3.5. Publication bias

Begg's funnel plots and the Egger test were performed to evaluate the publication bias of the selected literature. The shape of the

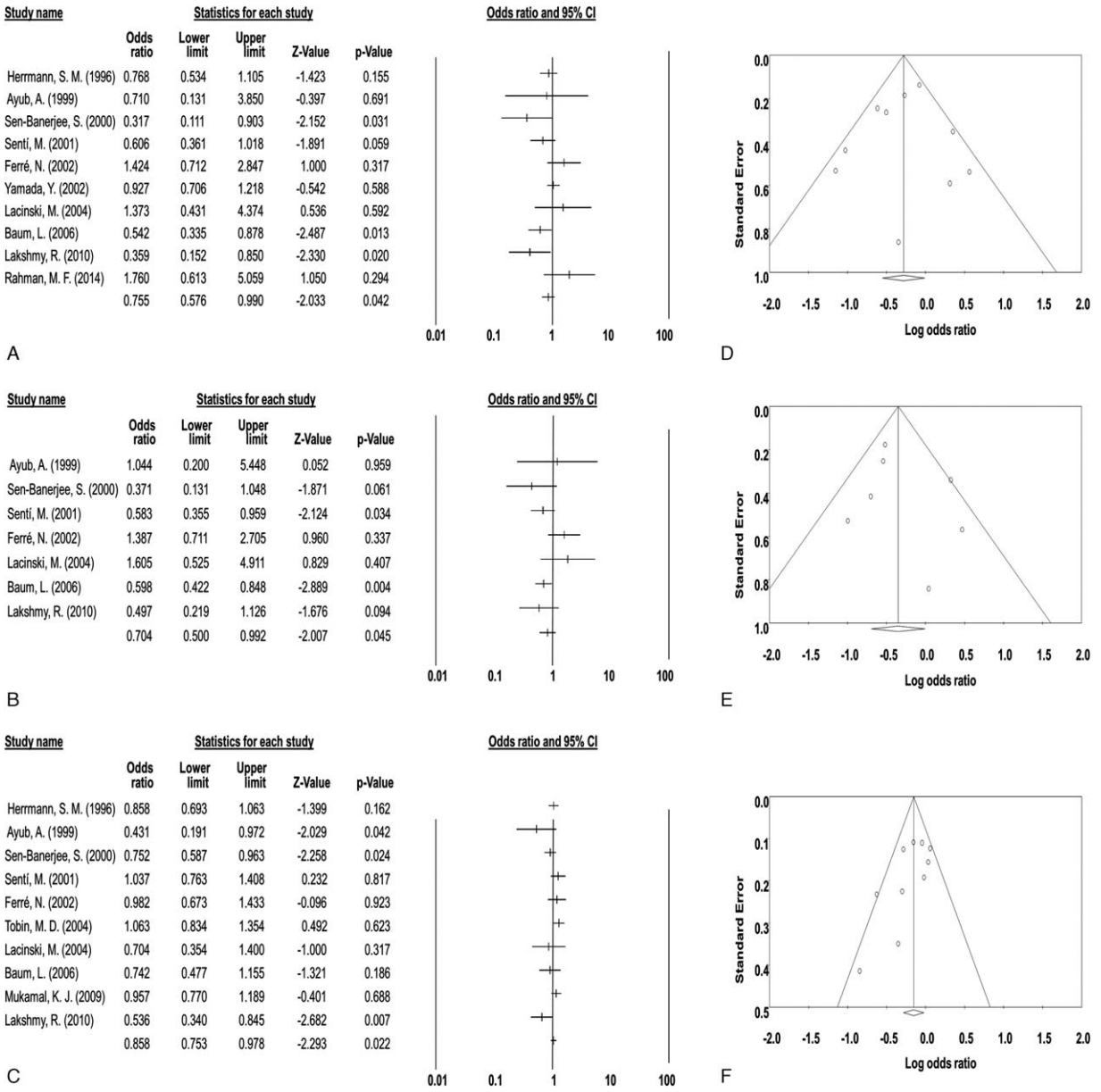

Figure 4. Results of analysis in MI population for Q192R polymorphism. A, B, and C showing the forest plot for genetic models: homozygote, dominant, and recessive, respectively; D, E, and F showing the funnel plot of publication biases with the genetic models above mentioned. MI = myocardial infarction.

funnel plot appeared to be symmetric (Figs. 1–6). The Egger test was then used to statistically assess funnel plot symmetry (Table 2). The results suggested no significant publication bias in all pooled studies.

4. Discussion

An increased lipid peroxidation is associated with a progression of heart diseases; however, the high-density lipoproteins (HDL) play an important role in protecting against these diseases due to their antioxidant properties. The main antioxidant enzyme carried by HDL particles is PON1.[3,7] The gene encoding human *PON1* has been cloned and sequenced; then several polymorphisms in its sequence have been identified. Specifically, L55M and Q192R polymorphisms have been associated with changes in protection against lipid peroxidation and with an altered risk of heart diseases.[17] Due to the above mentioned, *PON1* can be recognized as a heart disease susceptibility gene. In this study, 64 studies that had studied the correlation between *PON1* polymorphisms and heart diseases were collected and the effect of the variability on heart disease risk was analyzed by meta-analysis which is a useful tool to obtain clear and reliable results, very important in clinical and medical areas.[71,72] Our study systematically assessed the association between the L55M/Q192R polymorphisms of *PON1* gene and heart diseases risk in detail, based on a large sample (19,715 cases and 33,397 controls) and different gene contrast models, in the whole population as well as various subgroups. These features make this a more complete meta-analysis that previously published studies.[5,6,73] Moreover, other strength of our study is the quality of included studies which was evaluated by the NOS and GRADE scales and the results verified by the sensitivity analyses.

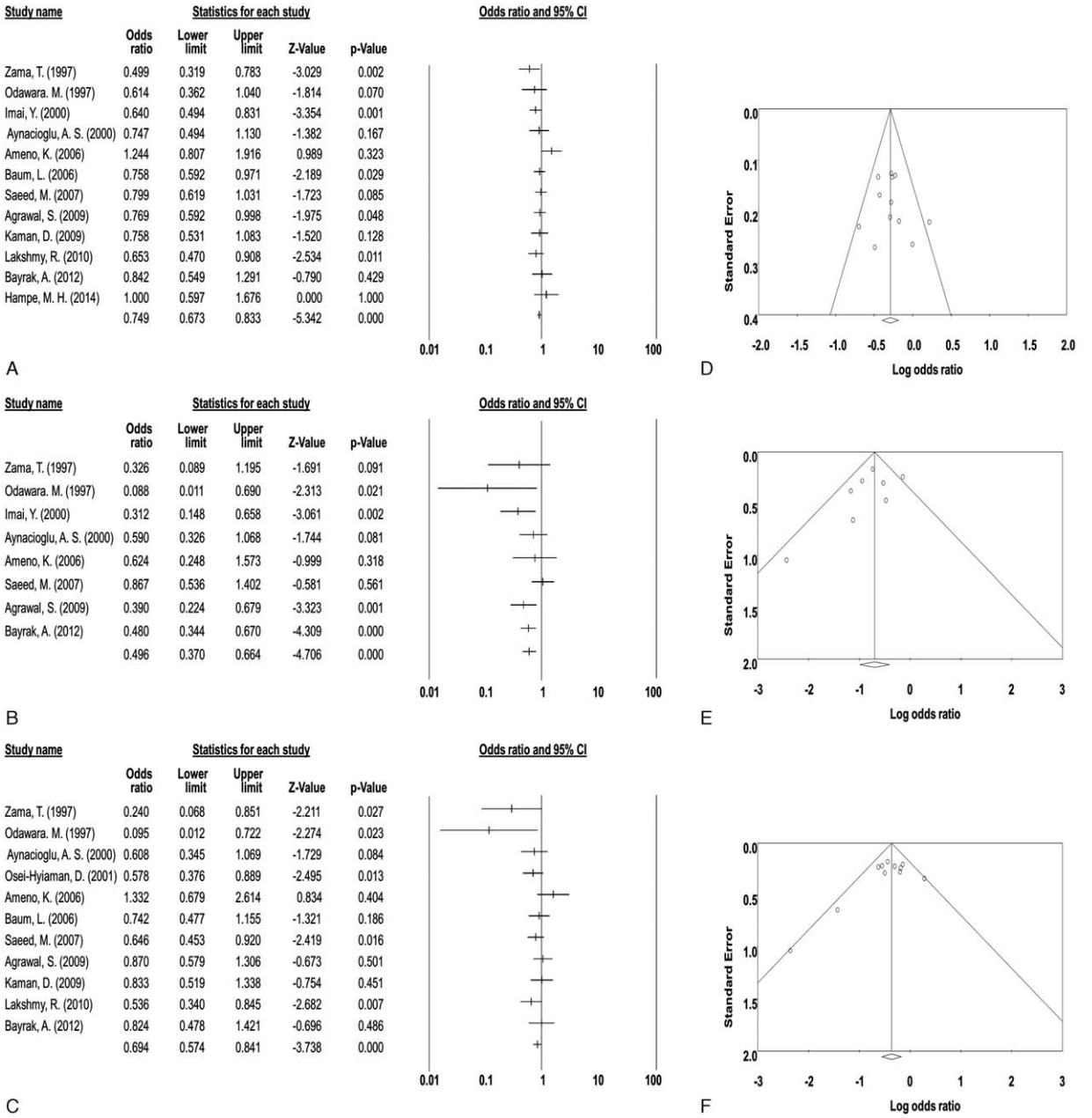

Figure 5. Results of analysis in Asian population for Q192R polymorphism. A, B, and C showing the forest plot for genetic models: allelic, heterozygote, and recessive, respectively; D, E, and F showing the funnel plot of publication biases with the genetic models above mentioned.

Overall, we found that the *PON1* L55M variant genotype was significantly associated with heart diseases risk based on random effect model in European and Asian populations, which is consistent with the results of Kaman et al, [31] Aydin et al,[33] Agrawal et al[3], and Zama et al[9]. On the other hand, when analyzed by subgroups (different diagnoses) no strong association was observed; possible explanations may be: the studied populations had different dietary habits and lifestyle, and the age and gender of the patients could also influence the studies. Furthermore, several studies support these findings, showing that *PON1* L55M polymorphism is not a predictor of CAD or MI.[17,18]

For the Q192R polymorphism, our meta-analysis demonstrated that individuals with the R allele have lower risk of suffering MI and CAD. Our findings are consistent with the previous results reported by Tobin et al[22] and Sanghera et al[7]. However, our analysis also showed that the Q allele is a risk allele for developing coronary artery disease. It can be argued that the Q allele may cause HDL-deficiency and therefore a low PON1 activity, reflecting a coexistent oxidative stress. Furthermore, it is known that HDL-deficiency states can increase the risk of MI.[8] In the subgroup analysis performed by ethnicity, the results showed that *PON1* Q192R polymorphism is associated with a low risk of heart diseases in Asian and African populations, but not among Europeans and Americans, implicating that ethnicity differences play an important role in the polymorphism effects. This single nucleotide polymorphism (SNP) could modify the oxidative function of lipoproteins and may play a role in heart diseases via a protective effect against lipoprotein oxidation.[11] Also, this SNP is more frequent in Asian populations (between

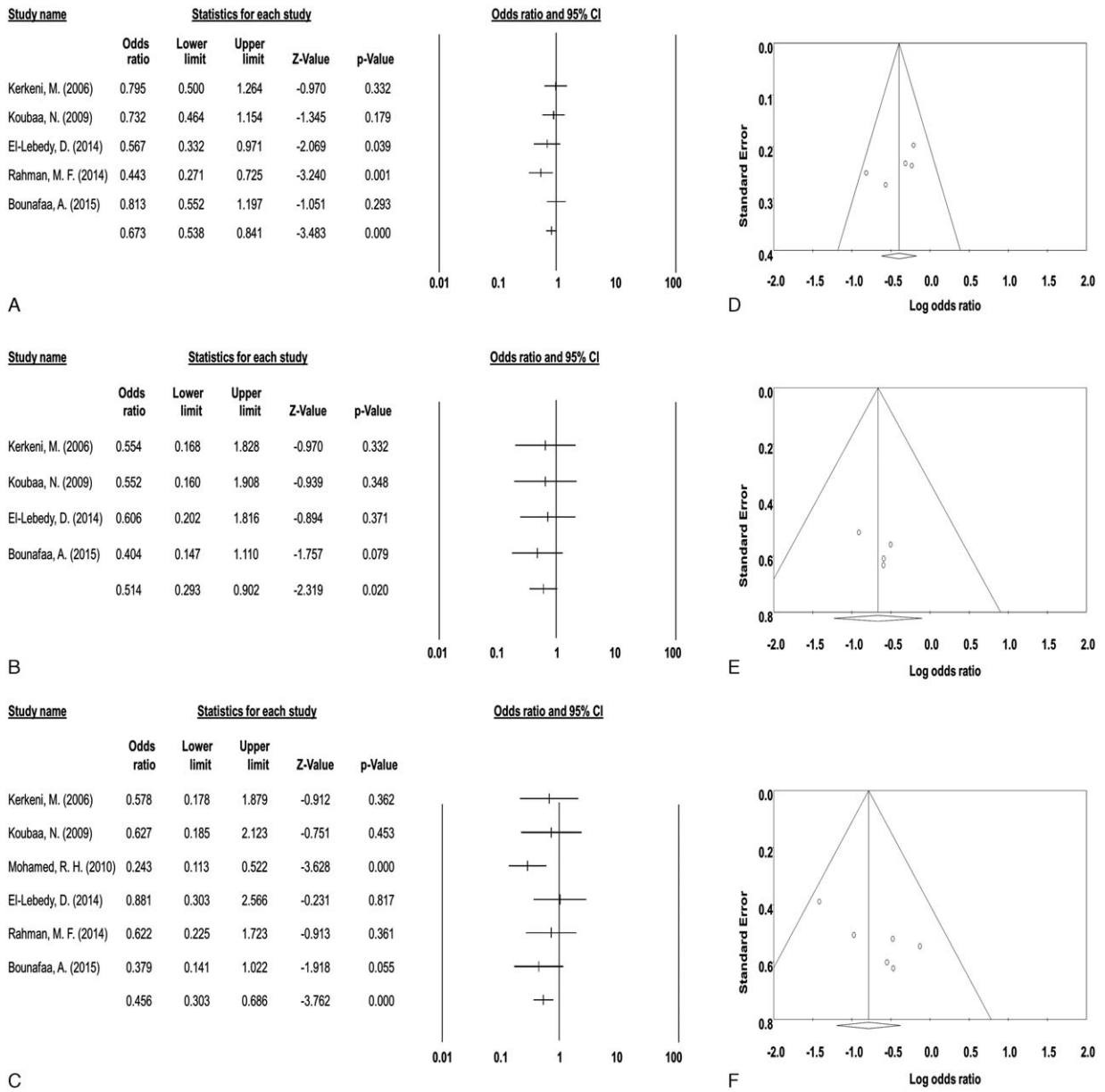

Figure 6. Results of analysis in African population for Q192R polymorphism. A, B, and C showing the forest plot for genetic models: allelic, homozygote and dominant, respectively; D, E, and F showing the funnel plot of publication biases with the genetic models above mentioned.

0.30 and 0.59);[4,9] while several studies have showed a no association of this polymorphism in others ethnicity groups.[12,31,60]

In interpreting the results, an important limitation of our study should be considered. It would have been valuable to stratify the results according to interactions among gene–gene and gene–-environment, though this was not possible, as the original data sets were not available. Despite this limitation, our meta-analyses also have some advantages: firstly, we included more studies than any previously published meta-analysis on the association between *PON1* polymorphism and heart diseases risk and secondly, we investigated two different *PON1* polymorphisms. In, summary, we performed a comprehensive analysis indicating that the genetic susceptibility for heart diseases is associated with *PON1* L55M polymorphism in European and Asian populations. As for the Q192R polymorphism, the R allele is involved in protection against heart diseases in Asian and African populations (specifically for coronary artery diseases and myocardial infarction). However, the Q allele may be a risk factor to develop CAD. Additionally, more well-studied association studies are needed to provide powerful evidence to the conclusions.

Acknowledgment

The authors thank all those who collaborated in the analysis, interpretation of data, and writing the article.

References

[1] Ravera A, Carubelli V, Sciatti E, et al. Nutrition and cardiovascular disease: finding the perfect recipe for cardiovascular health. Nutrients 2016;8:pii: E363.

[2] Ferrari R, Fox K. Heart rate reduction in coronary artery disease and heart failure. Nature reviews. Cardiology 2016;13:493–501.

[3] Agrawal S, Tripathi G, Prajnya R, et al. Paraoxonase 1 gene polymorphisms contribute to coronary artery disease risk among north Indians. Ind J Med Sci 2009;63:335–44.
[4] Ko YL, Ko YS, Wang SM, et al. The Gln-Arg 191 polymorphism of the human paraoxonase gene is not associated with the risk of coronary artery disease among Chinese in Taiwan. Atherosclerosis 1998;141: 259–64.
[5] Lawlor DA, Day IN, Gaunt TR, et al. The association of the PON1 Q192R polymorphism with coronary heart disease: findings from the British Women's Heart and Health cohort study and a meta-analysis. BMC Genet 2004;5:17.
[6] Zhao Y, Ma Y, Fang Y, et al. Association between PON1 activity and coronary heart disease risk: a meta-analysis based on 43 studies. Mol Genet Metab 2012;105:141–8.
[7] Sanghera DK, Saha N, Aston CE, et al. Genetic polymorphism of paraoxonase and the risk of coronary heart disease. Arterioscler Thromb Vasc Biol 1997;17:1067–73.
[8] Senti M, Tomas M, Marrugat J, et al. Paraoxonase1-192 polymorphism modulates the nonfatal myocardial infarction risk associated with decreased HDLs. Arterioscler Thromb Vasc Biol 2001;21:415–20.
[9] Zama T, Murata M, Matsubara Y, et al. A 192Arg variant of the human paraoxonase (HUMPONA) gene polymorphism is associated with an increased risk for coronary artery disease in the Japanese. Arterioscler Thromb Vasc Biol 1997;17:3565–9.
[10] Imai Y, Morita H, Kurihara H, et al. Evidence for association between paraoxonase gene polymorphisms and atherosclerotic diseases. Atherosclerosis 2000;149:435–42.
[11] Kuremoto K, Watanabe Y, Ohmura H, et al. R/R genotype of human paraoxonase (PON1) is more protective against lipoprotein oxidation and coronary artery disease in Japanese subjects. J Atheroscler Thromb 2003;10:85–92.
[12] Hasselwander O, Savage DA, McMaster D, et al. Paraoxonase polymorphisms are not associated with cardiovascular risk in renal transplant recipients. Kidney Int 1999;56:289–98.
[13] Ayub A, Mackness MI, Arrol S, et al. Serum paraoxonase after myocardial infarction. Arterioscler Thromb Vasc Biol 1999;19:330–5.
[14] Heijmans BT, Westendorp RG, Lagaay AM, et al. Common paraoxonase gene variants, mortality risk and fatal cardiovascular events in elderly subjects. Atherosclerosis 2000;149:91–7.
[15] Sen-Banerjee S, Siles X, Campos H. Tobacco smoking modifies association between Gln-Arg192 polymorphism of human paraoxonase gene and risk of myocardial infarction. Arterioscler Thromb Vasc Biol 2000;20:2120–6.
[16] Mackness B, Davies GK, Turkie W, et al. Paraoxonase status in coronary heart disease: are activity and concentration more important than genotype? Arterioscler Thromb Vasc Biol 2001;21:1451–7.
[17] Arca M, Ombres D, Montali A, et al. PON1 L55M polymorphism is not a predictor of coronary atherosclerosis either alone or in combination with Q192R polymorphism in an Italian population. Eur J Clin Investig 2002;32:9–15.
[18] Ferre N, Tous M, Paul A, et al. Paraoxonase Gln-Arg(192) and Leu-Met (55) gene polymorphisms and enzyme activity in a population with a low rate of coronary heart disease. Clin Biochem 2002;35:197–203.
[19] Yamada Y, Izawa H, Ichihara S, et al. Prediction of the risk of myocardial infarction from polymorphisms in candidate genes. N Engl J Med 2002; 347:1916–23.
[20] Robertson KS, Hawe E, Miller GJ, et al. Human paraoxonase gene cluster polymorphisms as predictors of coronary heart disease risk in the prospective Northwick Park Heart Study II. Biochim Biophys Acta 2003; 1639:203–12.
[21] Oliveira SA, Mansur AP, Ribeiro CC, et al. PON1M/L55 mutation protects high-risk patients against coronary artery disease. Int J Cardiol 2004;94:73–7.
[22] Tobin MD, Braund PS, Burton PR, et al. Genotypes and haplotypes predisposing to myocardial infarction: a multilocus case-control study. Eur Heart J 2004;25:459–67.
[23] Martinelli N, Girelli D, Olivieri O, et al. Interaction between metabolic syndrome and PON1 polymorphisms as a determinant of the risk of coronary artery disease. Clin Exp Med 2005;5:20–30.
[24] Kerkeni M, Addad F, Chauffert M, et al. Hyperhomocysteinemia, paraoxonase activity and risk of coronary artery disease. Clin Biochem 2006;39:821–5.
[25] Blatter Garin MC, Moren X, James RW. Paraoxonase-1 and serum concentrations of HDL-cholesterol and apoA-I. J Lipid Res 2006; 47:515–20.
[26] Rios DL, D'Onofrio LO, Cerqueira CC, et al. Paraoxonase 1 gene polymorphisms in angiographically assessed coronary artery disease: evidence for gender interaction among Brazilians. Clin Chem Lab Med 2007;45:874–8.
[27] Saeed M, Perwaiz Iqbal M, Yousuf FA, et al. Interactions and associations of paraoxonase gene cluster polymorphisms with myocardial infarction in a Pakistani population. Clin Genet 2007;71: 238–44.
[28] Troughton JA, Woodside JV, Yarnell JW, et al. Paraoxonase activity and coronary heart disease risk in healthy middle-aged males: the PRIME study. Atherosclerosis 2008;197:556–63.
[29] Ozkok E, Aydin M, Babalik E, et al. Combined impact of matrix metalloproteinase-3 and paraoxonase 155/192 gene variants on coronary artery disease in Turkish patients. Med Sci Monit 2008;14: CR536–42.
[30] Birjmohun RS, Vergeer M, Stroes ES, et al. Both paraoxonase-1 genotype and activity do not predict the risk of future coronary artery disease; the EPIC-Norfolk Prospective Population Study. PloS ONE 2009;4: e6809.
[31] Kaman D, Ilhan N, Metin K, et al. A preliminary study of human paraoxonase and PON 1L/M55-PON 1Q/R 192 polymorphisms in Turkish patients with coronary artery disease. Cell Biochem Funct 2009;27:88–92.
[32] Koubaa N, Nakbi A, Hammami S, et al. Association of homocysteine thiolactonase activity and PON1 polymorphisms with the severity of acute coronary syndrome. Clin Biochem 2009;42:771–6.
[33] Aydin M, Gokkusu C, Ozkok E, et al. Association of genetic variants in methylenetetrahydrofolate reductase and paraoxonase-1 genes with homocysteine, folate and vitamin B12 in coronary artery disease. Mol Cell Biochem 2009;325:199–208.
[34] Mukamal KJ, Pai JK, Jensen MK, et al. Paraoxonase 1 polymorphisms and risk of myocardial infarction in women and men. Circ J 2009; 73:1302–7.
[35] Lakshmy R, Ahmad D, Abraham RA, et al. Paraoxonase gene Q192R & L55M polymorphisms in Indians with acute myocardial infarction & association with oxidized low density lipoprotein. Ind J Med Res 2010;131:522–9.
[36] Gupta N, Singh S, Maturu VN, et al. Paraoxonase 1 (PON1) polymorphisms, haplotypes and activity in predicting cad risk in North-West Indian Punjabis. PLoS ONE 2011;6:e17805.
[37] Bounafaa A, Berrougui H, Ghalim N, et al. Association between paraoxonase 1 (PON1) polymorphisms and the risk of acute coronary syndrome in a North African population. PloS ONE 2015;10:e0133719.
[38] Serrato M, Marian AJ. A variant of human paraoxonase/arylesterase (HUMPONA) gene is a risk factor for coronary artery disease. J Clin Investig 1995;96:3005–8.
[39] Antikainen M, Murtomaki S, Syvanne M, et al. The Gln-Arg191 polymorphism of the human paraoxonase gene (HUMPONA) is not associated with the risk of coronary artery disease in Finns. J Clin Investig 1996;98:883–5.
[40] Suehiro T, Nakauchi Y, Yamamoto M, et al. Paraoxonase gene polymorphism in Japanese subjects with coronary heart disease. Int J Cardiol 1996;57:69–73.
[41] Herrmann SM, Blanc H, Poirier O, et al. The Gln/Arg polymorphism of human paraoxonase (PON 192) is not related to myocardial infarction in the ECTIM Study. Atherosclerosis 1996;126:299–303.
[42] Odawara M, Tachi Y, Yamashita K. Paraoxonase polymorphism (Gln192-Arg) is associated with coronary heart disease in Japanese noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metab 1997;82:2257–60.
[43] Ombres D, Pannitteri G, Montali A, et al. The gln-Arg192 polymorphism of human paraoxonase gene is not associated with coronary artery disease in italian patients. Arterioscler Thromb Vasc Biol 1998;18: 1611–6.
[44] Pati N, Pati U. Paraoxonase gene polymorphism and coronary artery disease in Indian subjects. Int J Cardiol 1998;66:165–8.
[45] Sanghera DK, Aston CE, Saha N, et al. DNA polymorphisms in two paraoxonase genes (PON1 and PON2) are associated with the risk of coronary heart disease. Am J Hum Genet 1998;62:36–44.
[46] Pfohl M, Koch M, Enderle MD, et al. Paraoxonase 192 Gln/Arg gene polymorphism, coronary artery disease, and myocardial infarction in type 2 diabetes. Diabetes 1999;48:623–7.
[47] Aynacioglu AS, Kepekci Y. The human paraoxonase Gln-Argl92 (Q/R) polymorphism in turkish patients with coronary artery disease. Int J Cardiol 2000;74:33–7.
[48] Aubo C, Senti M, Marrugat J, et al. Risk of myocardial infarction associated with Gln/Arg 192 polymorphism in the human paraoxonase gene and diabetes mellitus. The REGICOR Investigators. Eur Heart J 2000;21:33–8.

[49] Osei-Hyiaman D, Hou L, Mengbai F, et al. Coronary artery disease risk in Chinese type 2 diabetics: is there a role for paraxonase 1 gene (Q192R) polymorphism? Eur J Endocrinol 2001;144:639–44.
[50] Turban S, Fuentes F, Ferlic L, et al. A prospective study of paraoxonase gene Q/R192 polymorphism and severity, progression and regression of coronary atherosclerosis, plasma lipid levels, clinical events and response to fluvastatin. Atherosclerosis 2001;154:633–40.
[51] Scacchi R, Gambina G, Martini MC, et al. Different pattern of association of paraoxonase Gln192–>Arg polymorphism with sporadic late-onset Alzheimer's disease and coronary artery disease. Neurosci Lett 2003;339:17–20.
[52] Zee RY, Fernandez-Otiz A, Macaya C, et al. Lipid metabolism and occurrence of post-percutaneous transluminal coronary angioplasty restenosis: role of cholesteryl ester transfer protein and paraoxonase/arylesterase. J Thromb Haemost 2003;1:1202–7.
[53] Wang X, Fan Z, Huang J, et al. Extensive association analysis between polymorphisms of PON gene cluster with coronary heart disease in Chinese Han population. Arterioscler Thromb Vasc Biol 2003;23:328–34.
[54] Lacinski M, Skorupski W, Cieslinski A, et al. Determinants of homocysteine-thiolactonase activity of the paraoxonase-1 (PON1) protein in humans. Cell Mol Biol 2004;50:885–93.
[55] Ameno K, Ameno S, Kinoshita H, et al. Autopsy and postmortem examination case study on genetic risk factors for cardiac death: polymorphisms of endothelial nitric oxide synthase gene Glu298Asp variant and T-786C mutation, human paraoxonase 1 (PON1) gene and alpha2beta-adrenergic receptor gene. Vojnosanit Pregl 2006;63:357–61. discussion 362-353.
[56] Baum L, Ng HK, Woo KS, et al. Paraoxonase 1 gene Q192R polymorphism affects stroke and myocardial infarction risk. Clin Biochem 2006;39:191–5.
[57] Balcerzyk A, Zak I, Krauze J. Protective effect of R allele of PON1 gene on the coronary artery disease in the presence of specific genetic background. Dis Markers 2008;24:81–8.
[58] Bhattacharyya T, Nicholls SJ, Topol EJ, et al. Relationship of paraoxonase 1 (PON1) gene polymorphisms and functional activity with systemic oxidative stress and cardiovascular risk. JAMA 2008;299:1265–76.
[59] Gamboa R, Regalado JC, Huesca-Gomez C, et al. [Low paraoxonase and arylesterase plasma activities in Mexican patients with coronary artery disease]. Arch Cardiol Mex 2008;78:360–8.
[60] Izar MC, Helfenstein T, Ihara SS, et al. Association of lipoprotein lipase D9N polymorphism with myocardial infarction in type 2 diabetes: the genetics, outcomes, and lipids in type 2 diabetes (GOLD) study. Atherosclerosis 2009;204:165–70.
[61] Mohamed RH, Mohamed RH, Karam RA, et al. The relationship between paraoxonase1-192 polymorphism and activity with coronary artery disease. Clin Biochem 2010;43:553–8.
[62] Luu HN, Kingah PL, North K, et al. Interaction of folate intake and the paraoxonase Q192R polymorphism with risk of incident coronary heart disease and ischemic stroke: the atherosclerosis risk in communities study. Ann Epidemiol 2011;21:815–23.
[63] Elnoamany MF, Dawood AA, Azmy RM, et al. Paraoxonase 1 gene (Gln192–Arg) polymorphism and the risk of coronary artery disease in type 2 diabetes mellitus. Egypt Heart J 2012;64:55–62.
[64] Bayrak A, Bayrak T, Tokgozoglu SL, et al. Serum PON-1 activity but not Q192R polymorphism is related to the extent of atherosclerosis. J Atheroscler Thromb 2012;19:376–84.
[65] Hassan MA, Al-Attas OS, Hussain T, et al. The Q192R polymorphism of the paraoxonase 1 gene is a risk factor for coronary artery disease in Saudi subjects. Mol Cell Biochem 2013;380:121–8.
[66] Kang YH, Lao HY, Wu H, et al. Association of PON1 genotype and haplotype with susceptibility to coronary artery disease and clinical outcomes in dual antiplatelet-treated Han Chinese patients. Eur J Clin Pharmacol 2013;69:1511–9.
[67] Hampe MH, Mogarekar MR. Paraoxonase1, its Q192R polymorphism and HDL-cholesterol in relation to intensive cardiac care unit stay in ischemic heart disease. Ind J Hum Genet 2014;20:51–8.
[68] El-Lebedy D, Kafoury M, Abd-El Haleem D, et al. Paraoxonase-1 gene Q192R and L55M polymorphisms and risk of cardiovascular disease in Egyptian patients with type 2 diabetes mellitus. J Diabetes Metab Disord 2014;13:124.
[69] Rahman MF, Hashad IM, Abou-Aisha K, et al. Addressing the link between paraoxonase-1 gene variants and the incidence of early onset myocardial infarction. Arch Med Sci 2015;11:513–20.
[70] Han Y, Dorajoo R, Ke T, et al. Interaction effects between Paraoxonase 1 variants and cigarette smoking on risk of coronary heart disease in a Singaporean Chinese population. Atherosclerosis 2015;240:40–5.
[71] Hernandez-Diaz Y, Tovilla-Zarate CA, Juarez-Rojop I, et al. The role of gene variants of the inflammatory markers CRP and TNF-alpha in cardiovascular heart disease: systematic review and meta-analysis. Int J Clin Exp Med 2015;8:11958–84.
[72] Gonzalez-Castro TB, Hernandez-Diaz Y, Juarez-Rojop IE, et al. The role of a Catechol-O-Methyltransferase (COMT) Val158Met genetic polymorphism in schizophrenia: a systematic review and updated meta-analysis on 32,816 subjects. Neuromol Med 2016;18:216–31.
[73] Wheeler JG, Keavney BD, Watkins H, et al. Four paraoxonase gene polymorphisms in 11212 cases of coronary heart disease and 12786 controls: meta-analysis of 43 sttudies. Lancet 2004;363:689–95.